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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
[illegible]	[illegible]	HAENSLER	[illegible]

HM12/0706

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EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1643	18

DATE MAILED: 07/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary

Application No.	Applicant(s)
08/836,576	Haensler et al.
Examiner	**Group Art Unit**
Brenda Brumback	1643

X Responsive to communication(s) filed on *05/20/99 and 06/09/99* .

X This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *25-86* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *25-86* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- ***SEE OFFICE ACTION ON THE FOLLOWING PAGES*** ---

DETAILED ACTION

1. The Amendment filed 05/20/99 and the Supplemental Amendment filed 06/09/99 have been received and made of record as Papers # 15 and 16 respectively. The Supplemental Information Disclosure Statement filed 06/09/99 has been received and made of record as Paper # 17. Claims 25, 30-34, 36-38, 43-47, 49, 55-59, 61, 71-75, 80, 82, and 84-86 have been amended. Claims 87 and 88 have been added. Pending claims are 25-88.

Claim Objections

2. The objection to claims 50-61 under 37 CFR 1.75(c), as being of improper dependent form as substantial duplicates of claims 25-36 is withdrawn. Applicant's arguments were persuasive.

Double Patenting

3. The provisional rejection of claims 25-86 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-49 of copending Application No. 08/903,978 is withdrawn, as this application has been abandoned.

Claim Rejections - 35 USC § 112

4. The rejection of claim 65 under 35 U.S.C. 112, first paragraph, is withdrawn. Applicant's arguments and supporting references submitted with paper # 17 were persuasive.

Claim Rejections - 35 USC § 103

5. The rejection of claims 25-86 under 35 U.S.C. 103(a) as being unpatentable over Bolcsak et al. (U.S. Patent 5,100,662) in view of Gao et al. (Biochemical and Biophysical Research Communications, 179:280-285, 1991) is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that Bolcsak fails to suggest the specifically recited compounds of claims 30-32. Claims 30-32 recite derivatized cholesterol compounds. Bolcsak teaches derivatized cholesterol compounds and provides extensive working examples describing methods of derivatizing cholesterol (see column 11, lines 33-40, and columns 20 and 21, Examples 1-5). Thus, absent some unexpected result from applicant's specific derivatized cholesterol compounds, Bolcsak suggests the compounds of the present invention.

Applicant argues that Bolcsak fails to suggest a method of specifically inducing a cytotoxic T cell or TH_1-type immune response. Bolcsak states that the vaccine art teaches the immune response to an immunogen as comprising stimulation of lymphocytes which include T-cells and that the immune response is divided into two facets for convenience, humoral and cell mediated (column 2, lines 25-46). The art teaches that a TH_1-type immune response is a humoral

response (see Couper et al., of record in paper # 12). These teachings would certainly seem to suggest T-cell and TH_1-type immune responses.

Applicant argues that Bolcsak teaches a structure requiring a chemical bridge, but fails to suggest that the chemical bridge should be a carbamyl group and also fails to suggest the neutral lipid of claim 35. Applicant's arguments are directed against this reference individually, where the rejection was based on the combination of Bolcsak with Gao et al. Gao teaches that a carbamoyl bridge enhances stability over compounds having an ester bond (page 285, lines 5-7). Gao specifically teaches the neutral lipid of claim 35. Applicant's argument that Gao fails to teach adjuvant activity is directed against the Gao reference individually, because this teaching is found in Bolcsak. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the Bolcsak and Gao references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the motivation to combine the references is found in the vaccine art. The vaccine art teaches that vaccines are either conventional or genetic. The art teaches that genetic

vaccines work by DNA transfection (see Gregoriadis, Dialog abstract, Pharm Res., 15[5]:661-70, 1998). Thus, one of ordinary skill in the art would have been motivated to combine a reference teaching liposome compositions having enhanced antigenicity (Bolcsak) with a reference teaching enhanced liposomal stability (Gao), because both references pertain to the vaccine art.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

6. The rejection of claims 25-86 under 35 U.S.C. 103(a) as being unpatentable over Popescu et al. (EPA 0 356 339) in view of Epand et al. (U.S. Patent 5,283,185) is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that Popescu fails to suggest a method for inducing a cytotoxic T-cell or TH_1-type immune response. Popescu teaches the immune response as twofold: cytotoxic (T-cell) and humoral. Popescu teaches that the humoral response is the production of immunoglobulins (see page 2, lines 20-48). As was discussed *supra*, the art teaches that production of immunoglobulins is a TH_1-type immune response. Popescu teaches that vaccines elicit both types

of responses. Therefore, it would seem that Popescu suggests vaccination for inducing a cytotoxic T-cell or TH_1-type immune response.

Applicant argues that Popescu fails to teach the recited compounds of claims 30-32; that Popescu fails to suggest combining the amphipathic compound and a neutral lipid; and that Popescu fails to teach a carbamoyl linkage. Once again, applicant's arguments are directed against the Popescu reference individually where the rejection was based on a combination of references. All of these components of applicant's claimed invention are taught in the Epand reference. Epand teaches that cholesterol derivatized compounds having an ester bond are unstable in solution and that the stability of these compounds is improved by a carbamoyl bond (see column 3, lines 1-6). Lastly, Epand teaches the neutral lipid and the specific compounds recited in claims 30-32 (see columns 15-16, claims 6-9).

Applicant argues that Popescu fails to to suggest administering the vaccine composition by either the mucosal or intranasal routes. Popescu teaches that administration of vaccines via a number of routes is standard in the art (page 9, last full paragraph). While Popescu is silent regarding specific administration by the intranasal or mucosal route, one of ordinary skill in the vaccine art would interpret a standard administration route as including intranasal or mucosal, especially when administering an immunogen for a respiratory virus, such as influenza. Thus, Popescu in combination with the knowledge available to one of ordinary skill in the art at the time the invention was made would have suggested mucosal or intranasal vaccination for a respiratory virus.

Applicant's arguments that the combination of Epand (DNA transfection) with Popescu (vaccination) cannot be properly combined have been addressed *supra* in the response to the argument against combining the Bolcsak and Gao references and are equally applicable to this combination.

The relevance of applicant's arguments regarding the Zhou reference are not completely understood. Epand teaches that the combination of the derivatized cholesterol, the neutral lipid, and the carbamoyl group yields compounds of enhanced stability in solution. The examiner can find no basis for applicant's assertion that Epand fails to teach a reasonable expectation of success using the neutral lipid in a vaccine composition. Rather the Epand teaching would seem to support its use in genetic vaccines. The relevance of the Zhou reference is unclear because it would seem that Zhou is teaching a different complex: DNA, lipopoly(L-lysine) and a co-lipid. Therefore, any conclusions regarding transfection efficiency of the one complex may not be relevant to the second.

Finally, applicant's argument that vaccine adjuvants function by a different mechanism that transfection agents is noted. However, the relevance of this argument to the instant rejection is not clear. Popescu teaches derivatized cholesterol vaccine adjuvants that suggest the claimed compositions. Epand teaches that the same derivatized cholesterol compounds are used in DNA vaccines and teaches that the combination of the derivatized cholesterol, the neutral lipid, and the carbamoyl group results in a molecule that is more stable in solution. The art teaches that the

same compounds can be used in both types of vaccines. Absent some evidence or further explanation, it would seem that the mechanism by which they function in each case is irrelevant.

For these reasons, the outstanding rejections under 35 U.S.C. 103(a) are maintained.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Chris Eisenschenk whose telephone number is (703) 308-0452. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback,

Art Unit 1643 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1643 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
July 2, 1999

DONNA WORTMAN
PRIMARY EXAMINER